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RESEARCH ARTICLE

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Correlation of small nucleolar RNA host gene 16 with acute respiratory distress syndrome occurrence and prognosis in sepsis patients

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Abstract

Background: Long noncoding RNA small nucleolar RNA host gene 16 (lnc-SNHG16) regulates sepsis-induced acute lung injury and inflammation, which is involved in the pathophysiology of acute respiratory distress syndrome (ARDS). The present study intended to explore the role of lnc-SNHG16 as a potential biomarker indicating ARDS risk, disease severity, inflammation, and mortality in sepsis.

Methods: Peripheral blood mononuclear cell (PBMC) samples were collected from 160 sepsis patients within 24 hours after admission and 30 healthy controls (HCs). Then, lnc-SNHG16 in PBMCs was detected by reverse transcription-quantitative polymerase chain reaction. Sepsis patients were followed up until death or up to 28 days.

Results: lnc-SNHG16 was declined in sepsis patients compared with HCs ($p < 0.001$). The incidence of ARDS was 27.5% among sepsis patients; meanwhile, sepsis patients with ARDS had higher mortality than those without ARDS ($p < 0.001$). Furthermore, lnc-SNHG16 was declined in sepsis patients with ARDS compared to those without ARDS ($p < 0.001$); besides, higher lnc-SNHG16 was independently correlated with declined ARDS occurrence in sepsis patients ($p = 0.001$), while primary respiratory infection and higher CRP were independently correlated with elevated ARDS occurrence in sepsis patients (both $p < 0.05$). Moreover, a negative correlation was found in lnc-SNHG16 with history of diabetes, history of chronic obstructive pulmonary disease, and APACHE II and SOFA scores (all $p < 0.05$). Additionally, lnc-SNHG16 was declined in sepsis deaths compared with survivors ($p = 0.002$), while it was not independently linked with sepsis mortality.

Conclusion: lnc-SNHG16 correlates with lower ARDS occurrence and better prognosis in sepsis patients.

KEYWORDS
acute respiratory distress syndrome, disease severity, lnc-SNHG16, mortality, sepsis

1 | INTRODUCTION

Sepsis is considered a life-threatening disease worldwide, with acute respiratory distress syndrome (ARDS) as one of its major causes of death.[1,2] ARDS is a noncardiogenic pulmonary edema-stimulated respiratory failure syndrome, whose hallmark is diffusing alveolar injury caused by inflammation and lung endothelial cell dysfunction.[3,4] Currently, the treatments of ARDS include blood transfusion management, mechanical ventilation management, and nutritional support, while their efficacies are unsatisfactory.[5] Considering that the occurrence of ARDS is still elevating and the ARDS-caused mortality among sepsis patients remains high, it is urgent to explore potential biomarkers for the occurrence of ARDS, which might promote the management of sepsis patients with ARDS.[2]

Long noncoding RNA small nucleolar RNA host gene 16 (lnc-SNHG16) is located on chromosome 17q25.1 and encoded by a 7571-bp region.[6] Recently, many researchers have reported that lnc-SNHG16 takes part in the regulation of lung injury and inflammation, which are involved in the pathophysiology of sepsis-induced ARDS.[7–9] For instance, it has been presented that lnc-SNHG16 serves as competing endogenous RNA to promote lipopolysaccharide (LPS)-stimulated toll-like receptor 4 pathway, which participates in the progression of ARDS[10]; furthermore, lnc-SNHG16 regulates LPS-induced lung epithelial cell apoptosis via targeting microRNA (miR)-128-3p, consequently modulating lung injury[7]; meanwhile, it also has been reported that lnc-SNHG16 is able to regulate oxidative stress to regulate lung injury[11,12]; additionally, lnc-SNHG16 takes part in the regulation of cell apoptosis, autophagy, viability, and the production of proinflammatory cytokines in LPS-induced cells in human lung fibroblasts[8,9]; taken together, we deduced that lnc-SNHG16 might play an essential clinical role in ARDS stimulated by sepsis, while related data were obscured.

Thus, the current study aimed to explore the association of lnc-SNHG16 with ARDS occurrence, disease severity, and mortality risk in sepsis patients.

2 | METHODS

2.1 | Participants

This study enrolled 160 sepsis patients treated between October 2018 and June 2021. Enrolled patients were required to meet the following criteria: (a) diagnosed as sepsis in accordance with the third international consensus definitions for sepsis[13]; (b) aged 18–80 years; (c) were hospitalized within 24 h of symptom onset. Patients who had the following conditions were ineligible for recruitment: (a) had cancer or hematological malignancy; (b) complicated with autoimmune disease; (c) during pregnancy or breastfeeding. Additionally, the study also included 30 health subjects who had no abnormalities in medical examination as health controls (HCs). The exclusion criteria for HCs were identical with those for sepsis patients. The study was permitted by Ethics Committee of Zhongshan Hospital Affiliated to Xiamen University.

2.2 | Collection of data and samples

Clinical data of sepsis patients were recorded for subsequent analysis. Peripheral blood (PB) samples were collected from sepsis patients within 24 hours after admission, as well as from HCs after enrollment. Then, peripheral blood mononuclear cell (PBMC) samples were isolated using Ficoll PM400 (Cytiva, USA) to detect lnc-SNHG16 expression by reverse transcription-quantitative polymerase chain reaction (RT-qPCR).

2.3 | RT-qPCR assay

The RT-qPCR assay was performed for determining the lnc-SNHG16 in PBMCs. In brief, total RNA was extracted by TRIzol™ Reagent (Thermo Fisher Scientific, USA) and then reversely transcribed into cDNA using iScript™ cDNA Synthesis Kit (Bio-Rad, USA). Meanwhile, the qPCR was executed with KOD SYBR® qPCR Mix (Toyobo, Japan). The primers were designed according to a previous study.[14] Subsequently, the lnc-SNHG16 expression was analyzed using the $2^{-\Delta\Delta Ct}$ method (GAPDH as an internal control).

2.4 | Evaluation

After hospitalization, all sepsis patients received regular treatment in line with sepsis-3 international consensus[13] and were closely monitored for 28 days. Acute respiratory distress syndrome (ARDS) during hospitalization was recorded, which was diagnosed according to the American-European Consensus Conference on ARDS,[15] and mortality of patients during hospitalization was recorded as well.

2.5 | Statistics

SPSS (24.0 version, IBM Corp.) was employed for statistical analysis, and GraphPad Prism (6.01 version, GraphPad Software Lnc., USA) was applied for graph construction. Difference analysis between two groups was conducted using the Mann–Whitney U test. Correlation analysis between two variables was determined using chi-squared test, the Mann–Whitney U test, the Kruskal–Wallis H rank-sum test, t test, or Spearman's rank correlation test. Receiver operating characteristic (ROC) curve was used to evaluate the distinguishing value of lnc-SNHG16 expression, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and Sequential Organ Failure Assessment (SOFA) score. Univariate logistic regression analysis was used to assess factors related to ARDS occurrence risk and 28-day mortality, and then all potential factors were

included in the multivariate logistic regression analysis with step forward method. $p < 0.05$ was considered as significant.

3 | RESULTS

3.1 | Clinical features of sepsis patients

Sepsis patients illustrated a mean age of 59.5 ± 5.7 years with 62 (38.8%) females and 98 (61.2%) males. Regarding medical history, there were 60 (37.5%) patients with a history of hypertension, 25 (15.6%) patients with a history of hyperlipidemia, and 17 (10.6%) patients with a history of chronic obstructive pulmonary disease (COPD). Moreover, the APACHE II and SOFA scores were 13.0 ± 6.1 and 4.5 ± 2.0, accordingly. Moreover, the median (interquartile range [IQR]) value of C-reactive protein (CRP) level was 72.6 (44.3–102.5) mg/L. Other clinical characteristics are displayed in Table 1.

3.2 | Comparison of lnc-SNHG16 between sepsis patients and HCs

Sepsis patients had lower lnc-SNHG16 than HCs (median (IQR): 0.423 (0.279–0.763) vs. 1.073 (0.673–1.589)) ($p < 0.001$) (Figure 1A). Moreover, lnc-SNHG16 possessed a good ability to discriminate sepsis patients from HCs with area under curve (AUC) (95% confidence interval [CI]) of 0.830 (0.747–0.912), which was presented by ROC curve (Figure 1B).

3.3 | ARDS occurrence and correlation of lnc-SNHG16 with ARDS in sepsis patients

The occurrence rate of ARDS was 27.5% in sepsis patients (Figure 2A). Moreover, the mortality rate was elevated in patients with ARDS (40.9%) compared to those without ARDS (14.7%) ($p < 0.001$) (Figure 2B). Besides, declined level of lnc-SNHG16 was found in patients with ARDS compared to those without ARDS (median (IQR): 0.280 (0.172–0.554) vs. 0.473 (0.317–0.832)) ($p < 0.001$) (Figure 2C). Additionally, lnc-SNHG16 was in possession of a certain ability to discriminate sepsis patients with ARDS from those without ARDS with AUC (95% CI) of 0.723 (0.635–0.811), which was presented by the ROC curve (Figure 2D). In addition, the ROC curve also presented that CRP had a certain ability to distinguish sepsis patients with ARDS from those without ARDS with AUC (95% CI) of 0.651 (0.554–0.747) (Figure S1); meanwhile, it also illustrated that APACHE II score did not have the ability to discriminate sepsis patients with ARDS from those without ARDS with AUC (95% CI) of 0.600 (0.498–0.702) (Figure S2A), while SOFA score had a certain ability to distinguish sepsis patients with ARDS from those without ARDS with AUC (95% CI) of 0.627 (0.521–0.734) (Figure S2B).

TABLE 1 Clinical characteristics

Items	Sepsis patients (*N* = 160)
Demographics	
Age (years), mean ± SD	59.5 ± 5.7
Gender, *n* (%)	
Female	62 (38.8)
Male	98 (61.2)
BMI (kg/m^2), mean ± SD	23.4 ± 3.3
Smoke, *n* (%)	51 (31.9)
Drink, *n* (%)	59 (36.9)
Medical history	
History of hypertension, *n* (%)	60 (37.5)
History of hyperlipidemia, *n* (%)	25 (15.6)
History of diabetes, *n* (%)	20 (12.5)
History of CKD, *n* (%)	13 (8.1)
History of CCVD, *n* (%)	32 (20.0)
History of asthma, *n* (%)	11 (6.9)
History of COPD, *n* (%)	17 (10.6)
Disease characteristics	
Primary infection site, *n* (%)	
Abdominal infection	61 (38.1)
Respiratory infection	40 (25.0)
Skin and soft tissue infection	22 (13.8)
Other infections	37 (23.1)
Primary organism, *n* (%)	
G− bacteria	83 (51.9)
G+ bacteria	41 (25.6)
Fungus	14 (8.8)
Others	25 (15.6)
Total culture negative	25 (15.6)
APACHE II score, mean ± SD	13.0 ± 6.1
SOFA score, mean ± SD	4.5 ± 2.0
Laboratory detection	
Scr (mg/dL), median (IQR)	1.8 (1.3–2.8)
Albumin (g/L), median (IQR)	24.5 (18.2–33.0)
WBC (10^9/L), median (IQR)	20.0 (13.4–28.3)
CRP (mg/L), median (IQR)	72.6 (44.3–102.5)
TNF-α (pg/ml), median (IQR)	140.3 (102.1–195.5)
IL-6 (pg/ml), median (IQR)	65.0 (52.0–92.3)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CCVD, cardiovascular and cerebrovascular diseases; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; G−, Gram-negative; G+, Gram-positive; IL-6, interleukin 6; IQR, interquartile range; Scr, serum creatinine; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; TNF-α, tumor necrosis factor alpha; WBC, white blood cell.

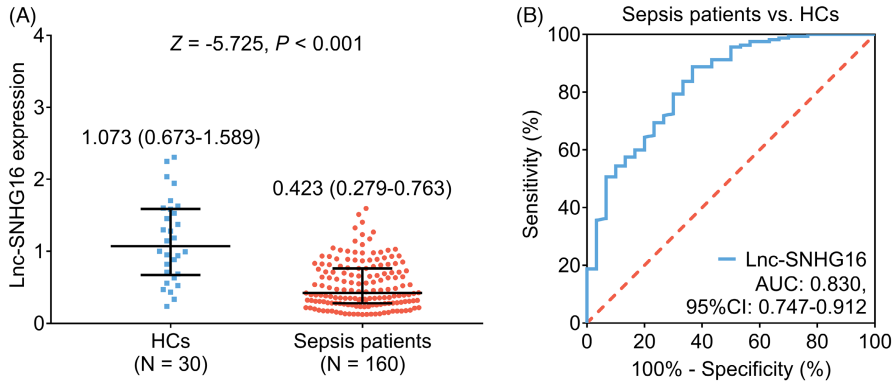

FIGURE 1 lnc-SNHG16 in sepsis patients and HCs. Comparison of lnc-SNHG16 between patients and HCs (A); capability of lnc-SNHG16 in discriminating patients from HCs (B). Abbreviations: AUC, area under curve; CI, confidence interval; HC, health controls; lnc-SNHG16, long noncoding RNA small nucleolar RNA host gene 16

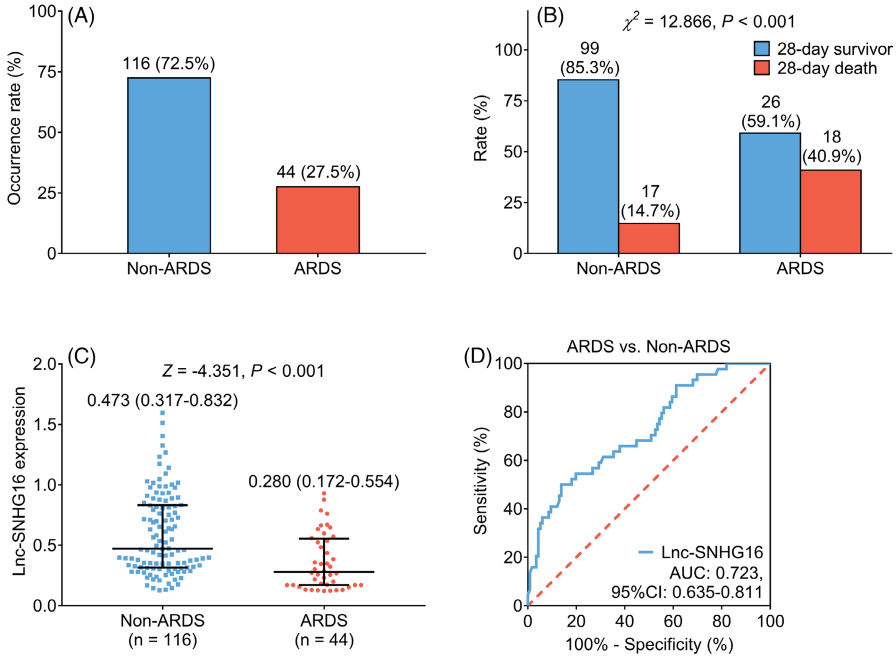

FIGURE 2 Capability of lnc-SNHG16 in predicting ARDS occurrence in sepsis patients. Occurrence rate of ARDS (A); mortality rate in patients with or without ARDS (B); comparison of lnc-SNHG16 between patients with ARDS and those without ARDS (C); the ability of lnc-SNHG16 in discriminating patients with ARDS from those without ARDS (D). Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; lnc-SNHG16, long noncoding RNA small nucleolar RNA host gene 16

3.4 | Factors related to the occurrence of ARDS in sepsis patients

Univariate logistic regression presented that higher lnc-SNHG16 was correlated with declined ARDS occurrence (odds ratio [OR] = 0.053, $p < 0.001$), while higher age, smoke, history of COPD, primary respiratory infection, higher APACHE II score, higher SOFA score, and higher CRP were related to increased ARDS occurrence (all OR >1, $p < 0.05$). Subsequent multivariate logistic regression illustrated that higher lnc-SNHG16 (OR = 0.061, $p = 0.001$) was independently correlated with lower ARDS occurrence, while higher age (OR = 1.089. $p = 0.023$), primary respiratory infection (OR = 3.850, $p = 0.007$), and higher CRP (OR = 1.009, $p = 0.042$) were all independently associated with higher ARDS occurrence (Table 2).

3.5 | Correlation of lnc-SNHG16 with medical history and disease features in sepsis patients

Negative correlation was discovered in lnc-SNHG16 with history of diabetes ($p = 0.012$) and history of COPD ($p = 0.043$). However, no correlation was found in lnc-SNHG16 with other medical history and disease features in sepsis patients (all $p > 0.05$) (Table 3).

3.6 | Correlation of lnc-SNHG16 with disease severity and mortality risk in sepsis patients

lnc-SNHG16 was negatively correlated with APACHE II score ($r_s = -0.316$, $p < 0.001$) (Figure 3A) and SOFA score ($r_s = -0.338$, $p < 0.001$) (Figure 3B). Moreover, sepsis deaths had lower lnc-SNHG16 than survivors (median (IQR): 0.353 (0.176–0.461) vs. 0.484 (0.290–0.828)) ($p = 0.002$) (Figure 3C). Additionally, lnc-SNHG16 was negatively correlated with APACHE II score ($r_s = -0.271$, $p = 0.002$) (Figure S3A) and SOFA score ($r_s = -0.229$, $p = 0.001$) (Figure S3B) among survivors; meanwhile, lnc-SNHG16 was not correlated with APACHE II score ($p = 0.473$) (Figure S3C) or SOFA score ($p = 0.372$) (Figure S3D) among deaths. Furthermore, sepsis deaths possessed a higher APACHE II score than survivors ($p < 0.001$) (Figure 3D); besides, sepsis deaths also had an increased SOFA score compared with survivors ($p < 0.001$) (Figure 3E). Subsequent ROC curve presented that lnc-SNHG16 had a certain ability to predict mortality

TABLE 2 Factors related to the risk of ARDS occurrence by logistic regression model analysis

Items	*p* value	OR	95%CI Lower	95%CI Upper
Univariate logistic regression				
Higher lnc-SNHG16	**<0.001**	0.053	0.011	0.248
Higher age	**0.024**	1.077	1.010	1.149
Gender (Male vs. Female)	0.986	1.007	0.494	2.053
Higher BMI	0.144	1.082	0.973	1.203
Smoke (Yes vs. No)	**0.025**	2.285	1.110	4.704
Drink (Yes vs. No)	0.776	1.109	0.543	2.268
History of hypertension (Yes vs. No)	0.584	1.220	0.600	2.482
History of hyperlipidemia (Yes vs. No)	0.132	1.980	0.814	4.820
History of diabetes (Yes vs. No)	0.186	1.926	0.729	5.088
History of CKD (Yes vs. No)	0.361	1.731	0.534	5.609
History of CCVD (Yes vs. No)	0.596	1.257	0.540	2.923
History of asthma (Yes vs. No)	0.177	2.350	0.679	8.136
History of COPD (Yes vs. No)	**0.004**	4.580	1.619	12.955
Primary infection site				
Abdominal infection	Ref.			
Respiratory infection	**0.003**	3.692	1.544	8.827
Skin and soft tissue infection	0.755	0.821	0.236	2.849
Other infections	0.776	0.862	0.309	2.403
Primary organism				
G− bacteria (Yes vs. No)	0.441	1.316	0.654	2.646
G+ bacteria (Yes vs. No)	0.358	0.675	0.292	1.561
Fungus (Yes vs. No)	0.925	1.060	0.314	3.573
Others (Yes vs. No)	0.303	1.607	0.652	3.964
Total culture negative (Yes vs. No)	0.670	0.806	0.299	2.173
Higher APACHE II score	**0.019**	1.070	1.011	1.132
Higher SOFA score	**0.004**	1.300	1.087	1.554
Higher Scr	0.295	1.122	0.905	1.390
Higher Albumin	0.305	0.982	0.948	1.017
Higher WBC	0.304	1.016	0.986	1.047
Higher CRP	**0.002**	1.012	1.004	1.019
Higher TNF-α	0.163	1.002	0.999	1.006
Higher IL-6	0.104	1.009	0.998	1.020
Multivariate logistic regression (Step forward method)				
Higher lnc-SNHG16	**0.001**	0.061	0.011	0.331
Higher age	**0.023**	1.089	1.012	1.172
Primary infection site				
Abdominal infection	Ref.			
Respiratory infection	**0.007**	3.850	1.439	10.298
Skin and soft tissue infection	0.576	1.497	0.364	6.149
Other infections	0.677	0.789	0.258	2.410
Higher CRP	**0.042**	1.009	1.000	1.017

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; BMI, body mass index; CCVD, cardiovascular and cerebrovascular diseases; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; G−, Gram-negative; G+, Gram-positive; IL-6, interleukin 6; lnc-SNHG16, long noncoding RNA small nucleolar RNA host gene 16; OR, odds ratio; Scr, serum creatinine; SOFA, Sequential Organ Failure Assessment; TNF-α, tumor necrosis factor alpha; WBC, white blood cell.

p values in bold indicates it has statistical significant.

risk in sepsis patients with AUC (95% CI) of 0.676 (0.581–0.771) (Figure 3F); meanwhile, APACHE II score and SOFA score both had a certain ability to predict mortality risk in sepsis patients with AUC (95% CI) of 0.788 (0.698–0.879) and 0.785 (0.689–0.881), accordingly (Figure 3G). Additionally, CRP also had a certain ability to predict mortality risk in sepsis patients with AUC (95% CI) of 0.684 (0.581–0.788) (Figure S4).

Subsequently, after adjustment by multivariate logistic regression, higher APACHE II score, higher SOFA score, and higher TNF-α were all independently correlated with increased mortality (all OR >1, $p \leq 0.01$) (Table 4).

4 | DISCUSSION

Despite great progress has been made in the understanding and management of ARDS, the incidence of ARDS remains high, especially in sepsis patients.[1,3] For instance, it has been reported that the incidence of ARDS is ranging from 6% to 7% among sepsis patients.[16,17] Thus, the exploration of potential biomarkers to indicate

TABLE 3 Correlation of lnc-SNHG16 expression with medical history and disease features in sepsis patients

Items	lnc-SNHG16, median (IQR)	Statistic (*Z*/*H*)	*p* value
History of hypertension			
No	0.380 (0.281–0.760)	−0.656	0.512
Yes	0.473 (0.271–0.826)		
History of hyperlipidemia			
No	0.415 (0.282–0.762)	−0.153	0.879
Yes	0.457 (0.224–0.810)		
History of diabetes			
No	0.468 (0.286–0.805)	−2.500	**0.012**
Yes	0.321 (0.187–0.422)		
History of CKD			
No	0.424 (0.282–0.752)	−0.181	0.856
Yes	0.385 (0.175–0.961)		
History of CCVD			
No	0.450 (0.283–0.760)	−0.424	0.671
Yes	0.372 (0.216–0.866)		
History of asthma			
No	0.437 (0.281–0.763)	−0.486	0.627
Yes	0.348 (0.172–0.910)		
History of COPD			
No	0.442 (0.286–0.770)	−2.021	**0.043**
Yes	0.302 (0.132–0.694)		
Primary infection site			
Abdominal infection	0.457 (0.236–0.820)	5.021	0.170
Respiratory infection	0.371 (0.282–0.645)		
Skin and soft tissue infection	0.649 (0.324–0.929)		
Other infections	0.398 (0.285–0.643)		
Primary organism			
G− bacteria	0.421 (0.268–0.705)	8.727	0.068
G+ bacteria	0.656 (0.325–0.913)		
Fungus	0.359 (0.227–0.452)		
Others	0.324 (0.217–0.697)		
Total culture negative	0.353 (0.280–0.692)		

Abbreviations: CCVD, cardiovascular and cerebrovascular diseases; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; G−, Gram-negative; G+, Gram-positive; IQR, interquartile range; lnc-SNHG16, long noncoding RNA small nucleolar RNA host gene 16.
p values in bold indicates it has statistical significant.

ARDS occurrence among sepsis is crucial, while only limited studies revealed that biomarker such as miR-23a-5p is correlated with a higher risk of ARDS in sepsis.[18] Until now, a variety of researches have reported that lnc-SNHG16 takes part in sepsis-induced acute lung injury and inflammation, which is involved in the pathogenesis of ARDS,[7–9] while the data about the clinical role of lnc-SNHG16 in sepsis-induced ARDS are obscured. Only one study reports that lnc-SNHG16 is declined in patients with respiratory disease such as coronavirus disease 2019 (COVID-19) compared with healthy populations.[19] In the current study, the incidence of ARDS was 27.5% among sepsis patients, which was numerically higher than that of previous study.[16,17] The potential explanation might be that different types of patients might lead to different incidences of ARDS. Besides, we also found that lnc-SNHG16 had a certain ability to discriminate sepsis patients with ARDS from those without ARDS; meanwhile, higher lnc-SNHG16 was an independent predictive factor for lower risk of ARDS in sepsis patients. The possible explanations might be that: (1) lnc-SNHG16 could inhibit acute lung injury via several methods (such as protecting lung epithelial cells from apoptosis through miR-128-3p-mediated high-mobility group box 3), which could suppress the development of ARDS[7,8]; (2) lnc-SNHG16 could activate γδ1 T cells, which led to declined inflammation and pulmonary fibrosis, subsequently inhibiting the occurrence of ARDS.[3,10,20]

Furthermore, we also found that lnc-SNHG16 was declined in sepsis patients with history of COPD and diabetes. The potential explanations might be that: (1) history of COPD could affect lung function, while lnc-SNHG16 could modulate lung injury;[7] thus, lnc-SNHG16 was dysregulated in sepsis patients with history of COPD; (2) history of diabetes resulted in dysregulated inflammation[21]; meanwhile, lnc-SNHG16 took part in the regulation of inflammation[22]; hence, aberrant lnc-SNHG16 expression was found in sepsis patients with history of diabetes. In addition, we also found that lnc-SNHG16 was negatively correlated with sepsis severity reflected by SOFA and APACHE II score, which might be caused by that lnc-SNHG16 could not only regulate multiple organ dysfunction but also systematic inflammation, which would lead to decreased disease severity of sepsis.[7,23–25]

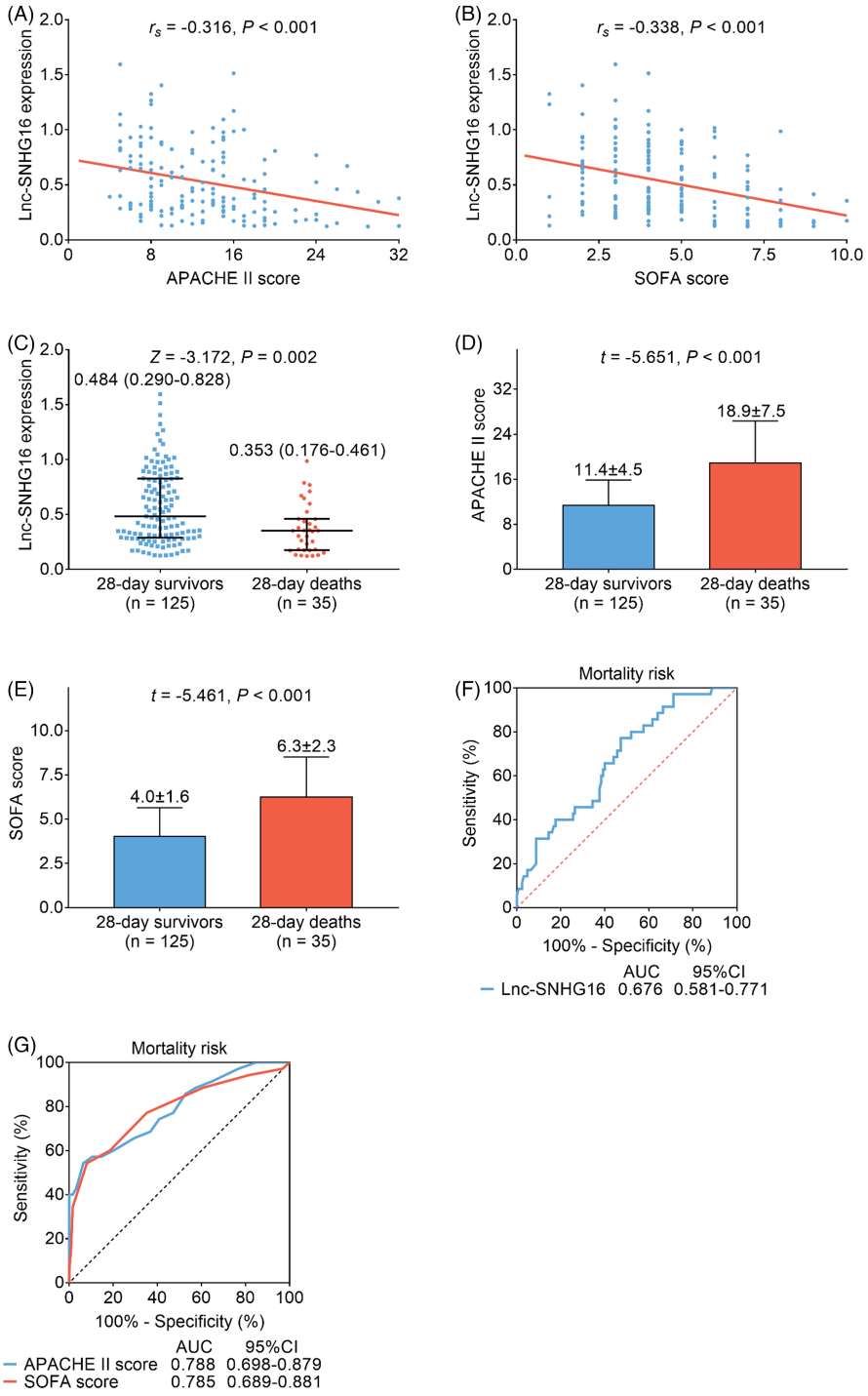

FIGURE 3 Association of lnc-SNHG16 with APACHE II and SOFA scores and their abilities to predict mortality in sepsis patients. Correlation of lnc-SNHG16 with APACHE II (A) and SOFA (B) scores; comparison of lnc-SNHG16 (C), APACHE II (D) and SOFA (E) scores between 28-day survivors and 28-day deaths; the ability of lnc-SNHG16 (F), APACHE II and SOFA (G) scores in predicting mortality risk in patients. Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; AUC, area under curve; CI, confidence interval; Lnc-SNHG16, long noncoding RNA small nucleolar RNA host gene 16; SOFA, Sequential Organ Failure Assessment

Currently, the main two predictors for sepsis mortality include SOFA and APACHE II scoring systems, while their assessment procedures are relatively complicated.[26,27] Thereby, the exploration of a convenient and accurate approach to predicting septic mortality is urgent and crucial to promoting the management of sepsis. In the current study, lnc-SNHG16 was declined in sepsis deaths compared with survivors. The possible explanation might be that lnc-SNHG16 could modulate systematic inflammation and multiple organ dysfunction, which led to decreased mortality of sepsis; thus, declined level of lnc-SNHG16 was found in sepsis deaths compared with survivors[7,23,25]; meanwhile, lnc-SNHG16 possessed a certain capacity of distinguishing deaths from survivals, whose ability was just numerically weaker than APACHE II score and SOFA score. However, lnc-SNHG16 was not independently linked with sepsis mortality. The potential explanation might be that the correlation of lnc-SNHG16 with sepsis mortality was affected by APACHE II score and SOFA score (independent factors of sepsis mortality). Thus, lnc-SNHG16 was not an independent factor for predicting mortality risk of sepsis.

Nevertheless, there existed several limitations in the current study: (1) lnc-SNHG16 was derived from PBMCs in patients and

TABLE 4 Factors related to 28-day mortality by logistic regression model analysis

Items	*p* value	OR	95%CI	
			Lower	Upper
Univariate logistic regression				
Higher lnc-SNHG16	**0.002**	0.081	0.016	0.401
Higher age	0.398	1.029	0.963	1.100
Gender (Male vs. Female)	0.340	0.691	0.324	1.475
Higher BMI	0.053	1.121	0.998	1.259
Smoke (Yes vs. No)	0.635	0.820	0.360	1.866
Drink (Yes vs. No)	0.665	1.185	0.550	2.556
History of hypertension (Yes vs. No)	0.730	1.145	0.531	2.467
History of diabetes (Yes vs. No)	**0.002**	4.600	1.731	12.225
History of CKD (Yes vs. No)	0.141	2.437	0.744	7.990
History of CCVD (Yes vs. No)	0.156	1.873	0.788	4.452
History of asthma (Yes vs. No)	0.655	1.371	0.344	5.468
History of COPD (Yes vs. No)	0.164	2.144	0.732	6.283
Primary infection site				
Abdominal infection	Ref.			
Respiratory infection	**0.006**	3.975	1.490	10.602
Skin and soft tissue infection	0.564	1.472	0.396	5.478
Other infections	0.274	1.828	0.621	5.379
Primary organism				
G− bacteria (Yes vs. No)	0.114	0.541	0.252	1.160
G+ bacteria (Yes vs. No)	0.391	0.669	0.267	1.674
Fungus (Yes vs. No)	0.198	2.148	0.670	6.884
Others (Yes vs. No)	0.068	2.358	0.938	5.929
Total culture negative (Yes vs. No)	0.187	1.882	0.735	4.820
Higher APACHE II score	**<0.001**	1.249	1.150	1.357
Higher SOFA score	**<0.001**	1.863	1.468	2.364
Higher Scr	**0.023**	1.293	1.036	1.614
Higher Albumin	0.946	0.999	0.963	1.036
Higher WBC	0.341	1.016	0.984	1.048
Higher CRP	**<0.001**	1.014	1.006	1.023
Higher TNF-α	**<0.001**	1.008	1.004	1.012
Higher IL-6	**0.047**	1.011	1.000	1.023
Multivariate logistic regression (Step forward method)				
Fungus (Yes vs. No)	**0.005**	13.479	2.206	82.346
Higher APACHE II score	**<0.001**	1.216	1.096	1.349
Higher SOFA score	**0.001**	1.632	1.216	2.191
Higher TNF-α	**<0.001**	1.011	1.005	1.017

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CCVD, cardiovascular and cerebrovascular diseases; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; G−, Gram-negative; G+, Gram-positive; IL-6, interleukin 6; lnc-SNHG16, long noncoding RNA small nucleolar RNA host gene 16; OR, odds ratio; Scr, serum creatinine; SOFA, Sequential Organ Failure Assessment; TNF-α, tumor necrosis factor alpha; WBC, white blood cell.

p values in bold indicates it has statistical significant.

controls, while we did not detect lnc-SNHG16 from other sources; (2) the longitudinal monitoring of lnc-SNHG16 dysregulation in sepsis patients could be explored in future to better investigate its clinical role in sepsis; (3) the current study lacked the investigation of the underlying mechanism of lnc-SNHG16 in the pathogenesis of sepsis-induced ARDS, which could be explored in the further study.

To be conclusive, lnc-SNHG16 correlates with lower ARDS risk, declined severity, and less mortality in sepsis patients, whose measurement may contribute to sepsis management.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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